Biochemical Pharmacology, Vol. 36, No. 8, pp. 1297–1302, 1987.
Printed in Great Britain.

0006-2952/87 $3.00 + 0.00

BETA-ADRENERGIC RESPONSIVENESS AND CARDIAC AUTONOMIC RECEPTORS AFTER IMPLANTATION OF THE MtTW15 PITUITARY ADENOMA IN THE RAT

CAROL A. NELSON,*† MICHAEL J. KATOVICH‡ and STEPHEN P. BAKER*§

Departments of *Pharmacology and ‡Pharmacodynamics, Colleges of Medicine and Pharmacy, University of Florida, Gainesville, FL 32610, U.S.A.

(*Received* 3 *April* 1986; *accepted* 2 *September* 1986)

Abstract—The effects of chronic MtTW15 pituitary adenoma implantation on beta-adrenergic responsiveness, cardiac beta-adrenoreceptors, and muscarinic receptors were studied in the rat. Five weeks after s.c. administration of tissue fragments of the MtTW15 adenoma, there was a 51 and 20% increase in the heart weight and body weight, respectively, and a 49-fold increase in the serum prolactin level as compared to the controls. At this time there was also an attenuation in the adenoma-bearing group of the ability of isoproterenol to produce a dipsogenic response and to increase the heart rate. In contrast, isoproterenol stimulated cardiac ornithine decarboxylase (ODC) activity 4.2-fold in both the control and adenoma-bearing groups. There was no change between the two groups in the cardiac ventricular beta-adrenoreceptor or muscarinic receptor concentration as measured by specific (−)-[^{125}I]iodocyanopindolol (CYP) and (−)-[^{3}H]quinuclidinyl benzilate (QNB) respectively. In addition, the concentrations of isoproterenol and carbachol required to inhibit by 50% (IC_{50}) [^{125}I]CYP and [^{3}H]QNB binding, respectively, in the absence of 5′-guanylylimidodiphosphate (Gpp(NH)p) were not different between the two groups. In the presence of Gpp(NH)p, the isoproterenol IC_{50} value was not different between the two groups, whereas the carbachol IC_{50} value was increased slightly in the adenoma-bearing group. The data indicate that chronic MtTW15 adenoma implantation attenuated beta-mediated dipsogenic and heart rate responses but had little or no effect on cardiac ODC activity or cardiac autonomic receptor concentrations and agonist binding properties.

Beta-adrenergic responsiveness has been shown to decline in rats inoculated with the transplantable MtTW15 pituitary adenoma. The decreased responses include isoproterenol-induced thirst, the positive cardiac chronotropic response to beta-adrenergic agonists, and the elevation in tail skin temperature induced by beta-adrenergic stimulation [1–3]. The decline in responsiveness usually begins within 3 weeks after adenoma implantation and becomes maximal at 6 weeks [1, 3]. Furthermore, this hypoadrenergic state was found to be reversible since removal of the adenoma tissue is followed by the recovery of the beta-adrenergic responsiveness [2].

It is currently unknown whether the adenoma-induced attenuation of beta-responsiveness is mediated by one of the primary hormones secreted by the adenoma, one of the secondary hormones influenced by the adenoma tissue, or some combination thereof. The primary hormones secreted include prolactin and growth hormone [4, 5], and the secondary hormones affected by the MtTW15 adenoma include insulin [6], glucagon [6], testosterone [5, 7], luteinizing hormone [7] and thyroid hormone [2, 8]. Regardless of a possible relationship between adenoma hormonal effects and beta-responsiveness, the alterations in beta-mediated responses could be partly accounted for by changes at the autonomic receptor level. Therefore, in the present study several types of beta-adrenergic responses, beta-adrenoreceptors, and muscarinic cholinergic receptors were determined after chronic MtTW15 adenoma implantation.

MATERIALS AND METHODS

Materials. (−)-[^{125}I]Iodocyanopindolol (2200 Ci/mmole) was purchased from the Amersham Corp., Arlington Heights, IL. (−)-[^{3}H]Quinuclidinyl benzilate (30.2 Ci/mmole), L-[^{14}C]ornithine (52.7 mCi/mmole) and Protosol were obtained from the New England Nuclear Corp., Boston, MA. Atropine, (±)alprenolol, isoproterenol, 5′-guanylyl-imidodiphosphate, dithiothreitol and pyridoxal phosphate were purchased from the Sigma Chemical Co., St. Louis, MO.

Animal treatment. Seventy male Wistar–Furth rats weighing between 100 and 150 g were housed in hanging stainless steel cages in groups of two. The room was illuminated from 5:00 a.m. to 7:00 p.m. and maintained at 25°. Animals were allowed free access to food and tap water. Thirty-five of the rats were injected subcutaneously (s.c.) in the center of the back with tissue fragments of the MtTW15 anterior pituitary adenoma [4]. These animals remained relatively healthy after induction of the MtTW15 tissue fragments and gained more weight than the control animals. Physiological responses and biochemical assays were performed 5 weeks after adenoma inoculation.

† Present address: National Institutes of Health, Building 29A, 8800 Rockville Pike, Bethesda, MD 20014.

§ Address correspondence to: Stephen P. Baker, Ph.D., Department of Pharmacology, University of Florida, College of Medicine, JHMHC, Box J-267, Gainesville, FL 32610.

Membrane preparation. Hearts from decapitated rats were quickly excised and rinsed in ice-cold saline for receptor assays. The atria were discarded, and the ventricles were blotted and weighed. For the beta-adrenoreceptor assays, the tissue was minced with scissors and homogenized in 10 ml of ice-cold 50 mM Tris–HCl containing 10 mM $MgCl_2$ at pH 7.4 with a Tekmar SDT-100EN homogenizer at setting 3 for 15 sec. For the muscarinic-cholinergic receptor assays, minced ventricles were homogenized in 10 ml of ice-cold 50 mM Tris–HCl at pH 7.4 containing 10 mM $MgCl_2$ and 320 mM sucrose for 15 sec at setting 3. The suspensions were then diluted with an additional 20 ml of their respective ice-cold homogenization buffers and centrifuged at 48,000 *g* for 10 min. The supernatant fractions were discarded, and the pellets were resuspended in 30 ml of ice-cold homogenization buffer (setting 3, 5 sec). These suspensions were then passed through a nylon sieve (30 mesh) to remove large pieces of connective tissue and centrifuged as above. The resulting pellets were resuspended in 30 ml of ice-cold 50 mM Tris–HCl, pH 7.4, containing 10 mM $MgCl_2$ and centrifuged again at 48,000 *g* for 10 min. The final pellets were resuspended in 5 ml of the aforementioned buffer for assays. Protein contents were determined by the method of Lowry *et al.* [9] using bovine serum albumin as the standard.

Receptor assays. Cardiac beta-adrenoreceptors were determined by incubating membrane protein (50 μg/tube) in a total volume of 250 μl containing 50 mM Tris–HCl at pH 7.4, 10 mM $MgCl_2$, 6.25 to 100 pM (−)-[^{125}I]iodocyanopindolol (CYP) and with or without 1 μM (±)alprenolol for 1 hr at 36°. At the end of the incubation, 3 ml of 50 mM Tris–HCl containing 10 mM $MgCl_2$ at 37° was added to each tube, and the suspensions were poured over Whatman GF/C glass fiber filters under reduced pressure. Filters were washed quickly with an additional 6 ml of the same buffer, placed in scintillation vials, and counted. Specific ligand binding to the receptor was calculated as the difference between total binding in the absence of (±)alprenolol and the nonspecific binding determined in the presence of 1 μM (±)alprenolol. Specific binding was from 75 to 85% of the total ligand bound.

In some experiments, the abilities of various concentrations of (−)isoproterenol to inhibit specific [^{125}I]CYP binding were measured. Assays were the same as above except that the [^{125}I]CYP concentration was 30 pM and 0.1% ascorbic acid was added to the incubation mixture. These competitive binding assays were performed in the absence and presence of 100 μM 5′-guanylyl-imidodiphosphate (Gpp(NH)p).

Muscarinic receptors were determined by incubating membrane protein (250 μg) in a total volume of 2 ml containing 50 mM Tris–HCl at pH 7.4, 10 mM $MgCl_2$, 0.03 to 2 nM (−)-[^{3}H]quinuclidinyl benzilate (QNB) and with and without 1 μM atropine for 60 min at 36°. At the end of the incubation, 4 ml of ice-cold Tris–HCl at pH 7.4 containing 10 mM $MgCl_2$ was added to each tube after which its contents were rapidly poured over a Whatman GF/C glass fiber filter under reduced pressure. Each filter was washed with an additional 8 ml of ice-cold buffer, placed in a scintillation vial with 6 ml of Liquiscint (National Diagnostics, Somerville, NJ), and counted. Specific ligand binding was calculated as described above for the beta-adrenoreceptor. Agonist competition assays for the muscarinic receptor were performed as above, except that the concentration of [^{3}H]QNB was 0.25 nM and the concentration of carbachol was varied as indicated in the text.

Prolactin assays. Serum from trunk blood was collected from decapitated animals and frozen at −20°. All serum samples collected for determination of prolactin levels were obtained between 9:30 and 10:30 a.m. and were assayed using the double antibody radioimmunoassay kit supplied by the Hormone Distribution Program of the National Pituitary Agency (Bethesda, MD). All samples were assayed in triplicate and expressed in terms of the standard provided (RP-1).

Dipsogenic responses. All of the dipsogenic experiments began between 8:30 and 9:30 a.m. Animals were weighed and housed individually without food in stainless steel cages equipped with a 100-ml graduated, spillproof water bottle. Water levels were recorded during hr 1 and 2 after s.c. administration of 25 μg/kg (±)isoproterenol. Baseline dipsogenic responses were determined in each group by repeating this experiment within 2 days of each dipsogenic test and substituting saline (1 ml/kg) for the isoproterenol injection.

Chronotropic response. Heart rates were recorded on a Narco Bio Systems Inc. (Houston, TX) physiograph by securing electrocardiogram recording discs to a shaved area of the animal's chest with adhesive tape while they were lightly restrained in a wire mesh cage with a wooden floor. The control heart rate was measured 1 hr after restraint, after which 5 μg/kg (±)isoproterenol was administered s.c. Heart rates were recorded at intervals up to 60 min after the injection of isoproterenol. The data were analyzed by calculating the average heart rate at each time interval.

Ornithine decarboxylase (ODC) activity. Rats were decapitated 4 hr after a 100 μg/kg s.c. dose of (±)isoproterenol, since previous studies have shown this time to produce a maximal stimulation of the enzyme [10]. Basal ODC activity was determined 4 hr after a subcutaneous injection of saline. The hearts were rapidly removed after decapitation and rinsed in ice-cold saline. The atria were dissected off and the ventricles were homogenized (1 g tissue per 10 ml buffer) in 25 mM Tris–HCl buffer at pH 7.2 containing 0.5 mM dithiothreitol (DTT) and 50 μM pyridoxyl phosphate with a Tekmar homogenizer for 20 sec at setting 5. The homogenates were centrifuged at 40,000 *g* for 15 min, and the supernatant fraction was saved for the assay. Supernatant (200 μl) was added to 50 μl of 25 mM Tris–HCl buffer at pH 7.2 containing 0.5 mM DTT, 50 μM pyridoxyl phosphate and 60 μM [^{14}C]ornithine in an air-tight 10-ml side arm flask (Kontes, Vineland, NJ) and incubated for 60 min at 36°. The assay was stopped by adding 0.5 ml of 1 M citric acid to the incubation mixture. Protosol (0.2 ml) was added to the center well of the flask by syringe to absorb the $^{14}CO_2$. The flasks were incubated for an additional 30 min at 36°, after which the center wells were removed, placed

Table 1. Heart weights, body weights and serum prolactin levels of control and MtTW15 adenoma-bearing rats

	Heart wt (mg)	Body wt (g)	Heart/Body wt	Serum prolactin (ng/ml)
Control	709 ± 44	279 ± 7	2.62 ± 0.07	32.9 ± 11
Adenoma-bearing	1073 ± 34*	336 ± 9*	3.19 ± 0.06*	1625 ± 377*

Rats were injected s.c. with tissue fragments of the MtTW15 adenoma, and 5 weeks later the variables were measured. Data are the means ± SE, N = 6.
* Significantly different from the respective control ($P < 0.01$).

Table 2. Physiological responses to isoproterenol from control and MtTW15 adenoma-bearing rats

	Basal dipsogenic response (ml/kg·hr)	Dipsogenic response (ml/kg·hr) after (±)isoproterenol (25 μg/kg)	Basal cardiac ODC activity (nmoles/g·hr)	(±)Isoproterenol (100 μg/kg) stimulated cardiac ODC activity (nmoles/g·hr)
Control	3.1 ± 0.7	26.3 ± 1.5	2.51 ± 0.33	10.5 ± 0.7
Adenoma-bearing	2.5 ± 1.0	4.6 ± 1.1*	2.45 ± 0.71	10.5 ± 0.3

The responses were determined 5 weeks after s.c. inoculation with the MtTW15 adenoma. Data are the means ± SE, N = 6.
* Significantly different from the respective control ($P < 0.001$).

in scintillation fluid, and counted. Blanks were determined in the absence of or with boiled protein (100°, 10 min), both of which gave similar values.

Data analysis. The receptor concentrations and K_D values were determined from regression analysis of Scatchard [11] plots. The concentrations of agonists which inhibited ligand binding by 50% (IC_{50}) were determined using linear least squares analysis of Hill plots. The difference between the mean values of response variables from control and MtTW15 adenoma-bearing rats was computed using a two-tailed Student's *t*-test.

RESULTS

Physiological effects of MtTW15 adenoma implantation. As shown in Table 1, there was a 49-fold increase in the serum prolactin level 5 weeks after a subcutaneous inoculation of tissue fragments from the MtTW15 adenoma. At this time, the heart and body weights of the adenoma-bearing rats also were increased by 51 and 20% respectively. In addition, there was a 22% increase in the heart to body weight ratio in the adenoma-bearing rats, indicating that the adenoma promoted a cardiac hypertrophy (Table 1).

Table 2 shows the ability of isoproterenol to stimulate a dipsogenic response (25 μg (±)isoproterenol/kg) and to increase cardiac ODC activity (100 μg (±)isoproterenol/kg) after adenoma implantation for 5 weeks. The basal drinking levels and cardiac ODC activities were similar in the control and adenoma-bearing rats. After the administration of isoproterenol, the drinking level and ODC activity of the control rats increased 8.5- and 4.2-fold respectively. However, in the adenoma-bearing rats, isoproterenol administration only increased the drinking response by 1.8-fold whereas the ability of isoproterenol to increase cardiac ODC activity was

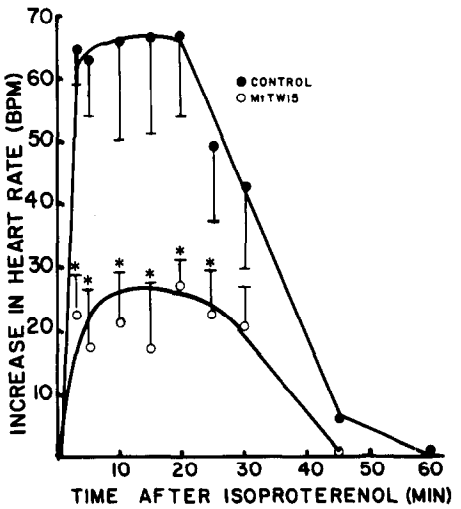

Fig. 1. Isoproterenol-stimulated mean heart rates in control and MtTW15 adenoma-bearing rats. (±)Isoproterenol (5 μg/kg) was administered s.c. to the control (●) and adenoma-bearing rats (○). At the times indicated, the heart rate was measured as described in Materials and Methods. Data are presented as the mean ± SE, N = 6. An asterisk indicates a significant difference from the control value at the same point ($P < 0.01$).

the same as in the control rats (4.3-fold). Figure 1 shows that the administration of (±)isoproterenol (5 μg/kg) rapidly elevated the heart rate in both control and adenoma-bearing rats. However, the magnitude of the chronotropic response to isoproterenol was attenuated by 66% in the MtTW15 adenoma-bearing rats as compared to the controls. The mean resting heart rate of the MtTW15 adenoma-bearing group was not significantly different from that of the control group (449 ± 8 and 451 ± 9

Table 3. Cardiac beta-adrenergic and muscarinic receptors from control and MtTW15 adenoma-bearing rats

	[^{125}I]CYP bound (fmoles/mg protein)	[^{125}I]CYP bound (fmoles/mg tissue)	K_D for [^{125}I]CYP binding (pM)	[^{3}H]QNB bound (fmoles/mg protein)	[^{3}H]QNB bound (fmoles/mg tissue)	K_D for [^{3}H]QNB binding (pM)
Control	25.1 ± 1.3	2.2 ± 0.1	23.5 ± 1.9	123.6 ± 6.0	8.2 ± 1.1	55.0 ± 6.9
Adenoma-bearing	26.9 ± 0.8	2.1 ± 0.09	18.1 ± 1.7	128.8 ± 8.3	7.0 ± 1.2	48.2 ± 44

The binding assays were performed 5 weeks after MtTW15 adenoma inoculation. The binding maximums and K_D values were determined by regression analysis of Scatchard plots. Data are the means ± SE, N = 6.

Table 4. Agonist binding characteristics to cardiac beta-adrenergic and muscarinic receptors from control and MtTW15 adenoma-bearing rats

	IC_{50} values for (−)-isoproterenol (nM)		IC_{50} values for carbachol (μM)	
	Minus Gpp(NH)p	Plus Gpp(NH)p (100 μM)	Minus Gpp(NH)p	Plus Gpp(NH)p (100 μM)
Control	25.3 ± 5.3	520 ± 80	8.1 ± 0.8	115 ± 10
Adenoma-bearing	18.5 ± 3.7	480 ± 25	12.9 ± 1.6	162 ± 20*

The competition assays were performed 5 weeks after MtTW15 adenoma implantation. The concentrations of agonist that inhibited ligand binding by 50% (IC_{50}) were determined from Hill plots. Data are means ± SE, N = 6.
* Significantly different from the control ($P < 0.05$).

beats per min respectively). The doses of isoproterenol chosen for the physiological responses are those that gave maximal effects in control rats.

Effect of adenoma-implantation on cardiac autonomic receptors. Table 3 shows that 5 weeks after MtTW15 adenoma implantation the concentrations of cardiac ventricular beta-adrenoreceptors ([^{125}I]CYP binding) and muscarinic receptors ([^{3}H]QNB binding) were not different from the control values. This lack of change was evident when the data were expressed as ligand bound per mg protein or per mg tissue. Furthermore, there was no difference in the K_D values for [^{125}I]CYP and [^{3}H]QNB binding between the two groups.

Table 4 shows the IC_{50} values for the inhibition of [^{125}I]CYP and [^{3}H]QNB binding to ventricular membranes by (−)-isoproterenol and carbachol respectively. In cardiac membranes from control and adenoma-bearing rats, Gpp(NH)p (100 μM) increased the (−)-isoproterenol IC_{50} value to a similar extent (21- to 26-fold). There was no significant difference in the absolute IC_{50} values both in the presence and absence of Gpp(NH)p between the two groups. The complete (−)-isoproterenol competition curves in the absence and presence of Gpp(NH)p are shown in Fig. 2. Table 4 also shows that Gpp(NH)p (100 μM) induced a 12- to 14-fold increase in the carbachol IC_{50} value for both groups. Although there was no difference between the two groups in the carbachol IC_{50} value obtained in the absence of Gpp(NH)p, in the presence of the guanine nucleotide there was a higher carbachol IC_{50} value in the adenoma-bearing group (162 ± 20 μM) than in the control group (115 ± 10 μM). The full carbachol competition curves in the presence and absence of Gpp(NH)p are shown in Fig. 3.

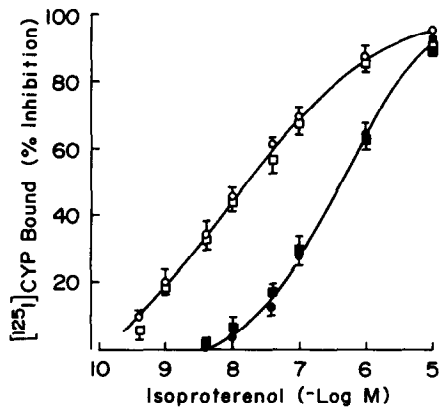

Fig. 2. Inhibition of specific [^{125}I]CYP binding by (−)-isoproterenol in cardiac membranes from control and MtTW15 adenoma-bearing rats. Membrane protein was incubated with 30 pM [^{125}I]CYP and the indicated concentration of (−)-isoproterenol for 60 min at 36°. Competition assays from control (circles) and adenoma-bearing (squares) animals were performed in the absence (open symbols) and presence (closed symbols) of 100 μM Gpp(NH)p. Each point on the graph is the mean ± SE. N = 6.

DISCUSSION

Similar to previous reports [1–3], we found in the present study that the ability of isoproterenol to induce a drinking response and increase the heart rate was greatly attenuated 5 weeks after MtTW15 adenoma implantation. To determine if receptor alterations were partly responsible for the attenuated beta-responsiveness in the heart, several characteristics of the beta-adrenoreceptor were deter-

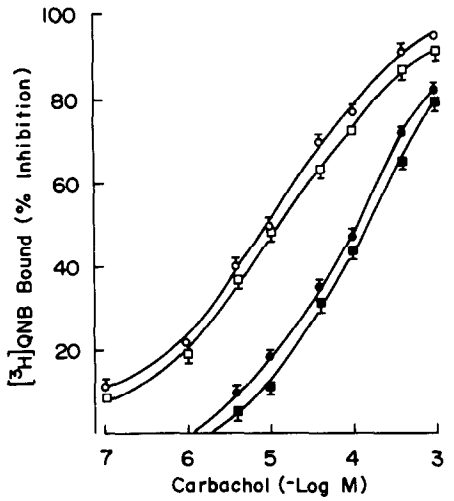

Fig. 3. Inhibition of specific [^{3}H]QNB binding by carbachol in cardiac membranes from control and MtTW15 adenoma-bearing rats. Membrane protein was incubated with 0.25 nM [^{3}H]QNB and the indicated concentration of carbachol for 60 min at 36°. Competition assays from control (circles) and adenoma-bearing (squares) animals were performed in the absence (open symbols) and presence (closed symbols) of 100 μM Gpp(NH)p. Each point on the graph is the mean ± SE, N = 6.

mined. Interestingly, there was no change in the cardiac ventricular beta-adrenoreceptor concentration or in the K_D value for [^{125}I]CYP binding between the control and adenoma-bearing group. Furthermore, the agonist competition curves and the ability of the guanine nucleotide Gpp(NH)p to reduce the agonist affinity were indistinguishable between the two groups. This suggested that there was no change in the ability of the receptor to form an agonist high-affinity binding state in the absence of the guanine nucleotide. Current evidence suggests that the agonist high-affinity binding state of the receptor observed in the absence of a guanine nucleotide represents a ternary complex formation of the agonist, receptor and a guanine nucleotide binding protein. The formation of the ternary complex appears to be necessary for receptor-mediated activation of adenylate cyclase to occur [12].

In contrast to beta-mediated stimulation of adenylate cyclase activity, it has been shown in cardiac tissue that muscarinic receptor activation can attenuate both basal and isoproterenol-induced enzyme activity [13, 14]. Thus, it is possible that part of the attenuated beta-responsiveness may have been due to an increase in cholinergic tone. However, there was no change between the two groups in the cardiac ventricular concentration of muscarinic receptors, the K_D value for [^{3}H]QNB binding, or the affinity of carbachol for the receptor in the absence of a guanine nucleotide. In the presence of Gpp(NH)p, there was a small but significant reduction in agonist affinity of the MtTW15-treated group, but it is not obvious how this would translate into a change of either cholinergic or beta-adrenergic responsiveness.

The lack of an adenoma-bearing effect on the properties of the cardiac beta-adrenoreceptor suggests that part of the mechanism for the attenuated cardiac beta-responsiveness must be beyond the receptor level. However, this possibility should be tempered for the following reason. The heart rate is controlled by the sino-atrial (S-A) nodal cells located in the atrial appendage, whereas the beta-adrenoreceptors were measured in ventricular tissue. Thus, in MtTW15 adenoma-bearing rats there may have been a selective alteration of the beta-adrenoreceptors in the S-A node. Unfortunately, it is not possible at this time to isolate pure S-A nodal cells to determine the receptor characteristics. In addition, a selective MtTW15-induced alteration in beta-responsiveness between the S-A node and ventricle was indicated by the lack of an adenoma effect on the ability of isoproterenol to stimulate ventricular ODC activity but an attenuation in the ability of the agonist to increase heart rate. If the mechanism of the MtTW15-adenoma effect on beta-responsiveness is related to the actions of one or several hormones released from the adenoma, then the indicated selective effect on beta-responsiveness may be due to the ability of the hormone(s) to only alter responsiveness in specific cell types (i.e. S-A nodal cells). The decreased beta-responsiveness in the MtTW15-treated rats could be partly explained by a change in the absorption, distribution or metabolism of isoproterenol altering the plasma concentration. However, this was unlikely since the isoproterenol-stimulated heart rate in both groups increased, plateaued, and declined as a function of time in a similar manner. Furthermore, it is possible that the attenuated heart rate response in the tumor-bearing rats may have been due to changes in the effects of isoproterenol directly on the heart and/or an indirect autoregulatory response. A change in the autoregulatory response may result from a tumor-induced cardiac hypertrophy leading to an increased cardiac output such that, as compared to control rats, a similar pressure and flow response after isoproterenol would be achieved with a smaller increase in heart rate. It should be pointed out, however, that the dipsogenic and vascular [1] responses to isoproterenol are not dependent on heart weight. Additionally, after removal of the tumor, when cardiac hypertrophy is still present, the cardiac response to isoproterenol is similar to controls [2]. Collectively, this suggests that a direct effect of isoproterenol on cardiac tissue is likely altered in the tumor-bearing rats.

Cardiac hypertrophy was indicated by an increase in the heart to body weight ratio 5 weeks after inoculation of rats with MtTW15 adenoma fragments in this and previous studies [1, 2]. Cardiac hypertrophy can be produced by aortic constriction, sympathetic hyperactivity, hyperthyroidism, and chronic stress or exercise [10, 15, 16]. In all of these instances, the increased heart weight was preceded by the stimulation of ODC activity, suggesting a causal relationship between cardiac growth and enzyme activation. Isoproterenol-induced cardiac hypertrophy has been shown to be blocked by α-difluoromethylornithine, a selective inhibitor of ornithine decarboxylase, without affecting the normal growth in mature rats [10]. Furthermore, both growth hormone and prolactin have been shown to elevate ODC

activity [17, 18]. The observation that basal levels of ODC were the same in control and MtTW15 adenoma-implanted rats could be due to a desensitization of ODC after weeks of chronic stimulation by prolactin and/or growth hormone. The cardiac hypertrophy observed 5 weeks after implantation of the MtTW15 adenoma which releases high levels of prolactin and growth hormone may be due to early elevation of ODC levels. Alternatively, a possible increase in blood volume accompanying a hyperprolactinemic state also could be responsible [1].

The thyroid status of the adenoma-bearing rats is unclear. Although the reported decreased serum levels of thyroxine [2] and thyroid stimulating hormone [5] would suggest a hypothyroid state, the serum level of triiodothyronine is not altered [2]. Furthermore, it has been well established that hypothyroidism decreases the chronotropic response to beta-agonists [19, 20], and reduces the concentration of cardiac beta-adrenoreceptors [20] and the formation of the agonist high-affinity binding state [21]. In contrast, hypothyroidism increases the cardiac ventricular concentration of muscarinic receptors [22] and increases the formation of the agonist high-affinity binding state [23]. Since these receptor changes did not occur in the adenoma-bearing rat, it is doubtful that a significant hypothyroid state existed and was responsible for the attenuated beta-responsiveness. Further studies are necessary to determine the mechanism of the adenoma-induced hypoadrenergic responsiveness.

In summary, the present study indicates that the MtTW15 adenoma can induce a decrease in beta-mediated heart rate increases and dipsogenic responses while not affecting beta-mediated cardiac ODC activity. Furthermore, little or no alterations in cardiac autonomic receptor concentrations or agonist binding properties occurred in the tumor-bearing rats.

Acknowledgements—This work was supported by National Institutes of Health Grants HL-27237, HL-32099 and GM-3409 (S.P.B.) and HD-18133 and HD-19742 (M.J.K.). The authors thank Ms. Susan Marchand and June O'Meara for their excellent technical support.

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